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D E C I S I O N
of 18 June 1998

Case Number: T 0151/95 - 3.3.2

Application Number: 89103091.8

Publication Number: 0330180

IPC: A61K 9/16

Language of the proceedings: EN

Title of invention:
Polylactic acid type microspheres containing physiologically active substance and process for preparing the same

Patentee:
Biomaterials Universe, Inc.

Opponent:
Boehringer Mannheim GmbH
Hoechst AG

Headword:
Microspheres/BIOMATERIALS UNIVERSE, INC.

Relevant legal provisions:
EPC Art. 52(1), 54, 56, 83, 114(1), (2)

Keyword:
"Novelty: yes "product-by-process" claim distinguished by the physical structure of the product from the prior art"
"Inventive step: yes, microspheres having a water soluble active substance incorporated into the polylactic acid matrix in a molecularly dispersed state not obviously derivable from the state of the art"

Decisions cited:
G 0009/91, G 0010/91, G 0004/95, T 0085/93, T 1002/92, T 0258/84, T 0273/84, T 0534/89, T 0205/83

Catchword:
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Case Number: T 0151/95 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 18 June 1998

Appellant: (Proprietor of the patent)
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Respondent: (Opponent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 27 January 1995 revoking European patent No. 0 330 180 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: G. F. E. Rampold
R. E. Teschemacher

Summary of Facts and Submissions

I. European patent No. 0 330 180 comprising 6 claims was granted on in response to European patent application No. 89 103 091.8.

Claim 1 reads as follows:

"A microsphere which comprises polylactic acid selected from the group consisting of an L-lactic acid polymer, a D,L-lactic acid polymer, a copolymer of L-lactic acid and glycolic acid and a copolymer of D,L-lactic acid and glycolic acid, and a water soluble physiologically active substance, selected from the group consisting of a polypeptide type or proteinaceous substance, an antimicrobial agent, an antitumor agent, an antipyretic, an antiinflammatory agent, an analgesic, an antitussive, an expectorant, an antidepressant, a muscle relaxant, an antiulcer agent, an antiallergic agent, a hypotensive, a diuretic, an antidiabetic, a cardiotonic, a vasodilating agent, an antiarrhythmic agent, an anticoagulating agent, a hemostatic agent, a narcotic antagonist, an antitubercular agent, a hormone, an immunoactivator, an antiepileptic agent, an antihistaminic and an agricultural agent, and has a mean particle size of from about 0.01 μm to 300 μm having not more than 30% of an eluted amount of said physiologically active substance based on the content of said physiologically active substance in the microsphere after 24 hours in in vitro elution test in phosphate buffer of pH 7.4 at 37° C."

II. Notice of opposition to the grant of the patent was filed

(i) by respondents 01 on 5 October 1993 requesting that the patent be revoked under Article 100(a) EPC on the grounds of lack of novelty (Articles 52(1), 54 EPC) and lack of inventive step (Articles 52(1), 56 EPC), and

(ii) by respondents 02 on 8 October 1993 requesting that the patent be revoked under Article 100(a) and (b) EPC on the grounds of lack of novelty (Articles 52(1), 54 EPC, lack of inventive step (Articles 52(1), 56 EPC) and insufficiency of disclosure of the invention (Article 83 EPC).

Out of the numerous documents submitted by the respondents in support of their requests within the nine month opposition period provided in Article 99(1) EPC, only the following remained relevant to the present decision in the appeal proceedings:

(1) EP-A-0 251 476;

(9) L. M. Sanders et al. "Controlled Delivery of an LHRH Analogue from Biodegradable Injectable Microspheres" in Journal of Controlled Release, 2 (1985), 187-195; in conjunction with reference 14 of (9): L.M. Sanders et al., J. Pharm. Sci. vol. 73, No. 9, (1984), 1294-1297;

(13) D. Hsie, "Controlled release systems, CRC Press, Inc., Boca Raton, Florida, 1988, 84-85;

During oral proceedings before the opposition division, respondents 01 cited additionally the following prior art document:

(14) US-A-4 389 330

III. The appellants (proprietors) requested during oral proceedings before the opposition division maintenance of the patent on the basis of the claims as granted as the main request or, alternatively, on the basis of an amended claim 1 submitted during the oral proceedings and claims 2 to 6 as granted.

Claim 1 of said auxiliary request read as follows:

"A microsphere which comprises polylactic acid selected from the group consisting of an L-lactic acid polymer, a D,L-lactic acid polymer, a copolymer of L-lactic acid and glycolic acid and a copolymer of D,L-lactic acid and glycolic acid, and a water soluble physiologically active substance, selected from the group consisting of a polypeptide type or proteinaceous substance, an antimicrobial agent, an antitumor agent, an antipyretic, an antiinflammatory agent, an analgesic, an antitussive, an expectorant, an antidepressant, a muscle relaxant, an antiulcer agent, an antiallergic agent, a hypotensive, a diuretic, an antidiabetic, a cardiotonic, a vasodilating agent, an antiarrhythmic agent, an anticoagulating agent, a hemostatic agent, a narcotic antagonist, an antitubercular agent, a hormone, an immunoactivator, an antiepileptic agent, an antihistaminic and an agricultural agent, wherein the hydrophilic physiologically active substance and hydrophobic polylactic acid are uniformly mingled in a molecular order, and has a mean particle size of from about 0.01 μm to 300 μm having not more than 30% of an eluted amount of said physiologically active substance based on the content of said physiologically active substance in the microsphere after 24 hours in in vitro elution test in phosphate buffer of pH 7.4 at 37^0 C obtainable by a process, which comprises preparing a solution of the water soluble physiologically active substance and the polylactic acid uniformly dissolved in a mixed solvent comprising a hydrophilic organic

solvent and water or in an organic acid, mixing the solution with a poor solvent immiscible with said mixed solvent or organic acid to give an O/O type or W/O type emulsion, and subjecting the emulsion to solvent evaporation drying."

IV. The patent was revoked pursuant to Article 102(1) EPC by the decision of the opposition division posted on 27 January 1995.

The opposition division saw in the respondents' submissions no basis for an opposition under Article 100(b) EPC to the main or to the auxiliary request on the grounds of insufficiency (Article 83 EPC).

Concerning the main request, the opposition division held that microspheres as defined in claim 1 did not contain any definite distinguishing technical feature over the prior art according to document (9) and were therefore not patentable on the grounds of lack of novelty.

On the other hand, the microspheres, which were defined more precisely in claim 1 of the auxiliary request by including the sequential steps of the process of their preparation as additional technical features, were held to be novel over (9) by virtue of the more homogeneous distribution or incorporation of the water soluble physiologically active agent in the polymer matrix material. This was acknowledged to be the result of the particular process of preparing said microspheres. However, in the absence of any recognisable technical effect associated with this more homogeneous distribution of the active agent, the opposition division considered the claimed microspheres merely as an obvious alternative to the state of the art

disclosed in (9) and therefore as lacking an inventive step.

The opposition division indicated in the reasons for the decision that it was able to come to the decision without taking into account the late-filed document (14).

V. The appellants (proprietors) filed an appeal against the above decision.

VI. In the annex to the summons to attend oral proceedings, the board considered that the insertion "wherein the hydrophilic physiologically active substance and hydrophobic polylactic acid are uniformly mingled in a molecular order" in claim 1 as amended was possibly not adequately supported by the originally filed documents and informed the parties that document (14) seemed *prima facie* sufficiently relevant to justify its admission into the proceedings. The parties were also informed that the opposition under Article 100(b) EPC on the grounds of insufficiency was in the board's preliminary opinion only insufficiently substantiated and inadequately supported by the arguments submitted on behalf of respondents 02.

VII. During oral proceedings before the board of appeal held on 18 June 1998, the appellants filed an amended statement of claim as the sole request, with claims 1 and 2 reading as follows:

"1. A microsphere which comprises polylactic acid selected from the group consisting of an L-lactic acid polymer, a D,L-lactic acid polymer, a copolymer of L-lactic acid and glycolic acid and a copolymer of D,L-lactic acid and glycolic acid, and a water soluble physiologically active substance, selected from the

group consisting of a polypeptide type or proteinaceous substance, an antimicrobial agent, an antitumor agent, an antipyretic, an antiinflammatory agent, an analgesic, an antitussive, an expectorant, an antidepressant, a muscle relaxant, an antiulcer agent, an antiallergic agent, a hypotensive, a diuretic, an antidiabetic, a cardiotonic, a vasodilating agent, an antiarrhythmic agent, an anticoagulating agent, a hemostatic agent, a narcotic antagonist, an antitubercular agent, a hormone, an immunoactivator, an antiepileptic agent, an antihistaminic and an agricultural agent, wherein the water-soluble physiologically active substance is uniformly incorporated into the polylactic acid, and has a mean particle size of from about 0.01 μm to 300 μm having not more than 30% of an eluted amount of said physiologically active substance based on the content of said physiologically active substance in the microsphere after 24 hours in in vitro elution test in phosphate buffer of pH 7.4 at 37^0 C obtainable by a process, which comprises preparing a solution of the water soluble physiologically active substance and the polylactic acid uniformly dissolved in a mixed solvent comprising a hydrophilic organic solvent and water or in an organic acid, mixing the solution with a poor solvent immiscible with said mixed solvent or organic acid to give an O/O type or W/O type emulsion, and subjecting the emulsion to solvent evaporation drying.

2. A process for preparing a microsphere which comprises polylactic acid selected from the group consisting of an L-lactic acid polymer, a D,L-lactic acid polymer, a copolymer of L-lactic acid and glycolic acid and a copolymer of D,L-lactic acid and glycolic acid, and a water soluble physiologically active substance, selected from the group consisting of a polypeptide type or proteinaceous substance, an antimicrobial agent, an antitumor agent, an

antipyretic, an antiinflammatory agent, an analgesic, an antitussive, an expectorant, an antidepressant, a muscle relaxant, an antiulcer agent, an antiallergic agent, a hypotensive, a diuretic, an antidiabetic, a cardiotonic, a vasodilating agent, an antiarrhythmic agent, an anticoagulating agent, a hemostatic agent, a narcotic antagonist, an antitubercular agent, a hormone, an immunoactivator, an antiepileptic agent, an antihistaminic and an agricultural agent, wherein the water-soluble physiologically active substance is uniformly incorporated into the polylactic acid, and and has a particle size of from about 0.01 μm to 300 μm having not more than 30% of an eluted amount of said physiologically active substance based on the content of said physiologically active substance in the microsphere after 24 hours in in vitro elution test in phosphate buffer of pH 7.4 at 37^0 C, which comprises preparing a solution of the water soluble physiologically active substance and the polylactic acid uniformly dissolved in a mixed solvent comprising a hydrophilic organic solvent and water or in an organic acid, mixing the solution with a poor solvent immiscible with said mixed solvent or organic acid to give an O/O type or W/O type emulsion, and subjecting the emulsion to solvent evaporation drying".

Dependent claims 3 to 5 are directed to specific embodiments of the process according to claim 2.

VIII. The appellants' submissions in support of their request, both in the written procedure and at the oral proceedings can essentially be summarised as follows:

Compared with claim 1 as granted the claimed microspheres were characterised in the present claim 1 by an additional technical feature reflecting the homogeneous incorporation of the active substance into the matrix in a molecularly dispersed state ("wherein

the water-soluble physiologically active substance is uniformly incorporated into polylactic acid") and were, moreover, defined by the particular method of their preparation. Such microspheres were not disclosed in any document cited by the respondents in the whole proceedings and were therefore novel. Incidentally, the novelty of the subject-matter of the contested patent, if defined in the form of a "product-by-process" claim, had already been acknowledged in paragraph 6 of the decision of the opposition division.

In particular, the release profiles of a representative number of microspheres, which were prepared according to the particular solvent evaporation method of the invention, provided clear evidence of the stable, continuous release of a broad range of water soluble physiologically active substances of different structure and size from the said microspheres. A comparison of these release profiles with the clear triphasic release profile of nafarelin disclosed in (9) demonstrated the novelty of the claimed microspheres in the contested patent vis-à-vis the state of the art according to (9).

With regard to the late-filed document (14), the appellants contended that the case should be remitted to the first instance, if the board reached the conclusion to admit (14) into the proceedings in view of its possible relevance to the decision.

Concerning the prior art of (14), the appellants referred to the long list of physiologically active substances mentioned in (14), which included in arbitrary order primarily water insoluble hydrophobic physiologically active substances and also certain water soluble hydrophilic active substances, and to the broad range of matrix materials mentioned in (14) likewise including in arbitrary order water soluble,

hydrophilic and water insoluble, hydrophobic materials. They referred also to the broad variety of solvents and, in this respect, particularly to the water immiscible solvents employed in (14) for the preparation of the solution or dispersion containing the active agent and the matrix material. The appellants considered the subject-matter of the present claims as a true selection from (14) and therefore as novel.

Starting from citation (9) as the closest state of the art, the technical problem the invention set out to solve was seen by the appellants as that of providing improved polylactic acid or mixed polylactic acid/polyglycolic acid type microspheres, which afforded, immediately following their application, continuous release of a water soluble physiologically active substance at a constant rate over an extended period of time.

None of the documents cited in the opposition or appeal proceedings suggested to a person skilled in the art how to solve this problem, let alone by the provision of the claimed microspheres in the contested patent. Such microspheres contained the physiologically active substance uniformly incorporated into the polylactide type matrix in a molecularly dispersed state, in spite of the fact that the active substance was hydrophilic and water soluble, whereas the matrix material was hydrophobic and insoluble in water.

Neither the provision of microspheres having this particular physical structure, let alone the method of their preparation, in particular the step of uniformly dissolving both components, namely the hydrophilic active substance and the hydrophobic matrix, in a mixed solvent comprising a hydrophilic organic solvent and

water or in an organic acid, was obvious to a person skilled in the art on the basis of the prior art available in the proceedings. The subject-matter of the contested patent, therefore, also involved an inventive step.

IX. The respondents disagreed. Their submissions, both in the written procedure and at the oral proceedings, can be summarised as follows:

The distinction made by the appellants between the microspheres as defined in claim 1 and those disclosed in the prior art of (9) was vague and indefinite. In particular, the newly introduced feature "wherein the water-soluble physiologically active substance is uniformly incorporated into the polylactic acid", was, contrary to the appellants' assertion, unclear and inappropriate for distinguishing the microspheres in the patent in suit from those disclosed in (9), because in (9) nafarelin was also in a certain manner "uniformly incorporated" in the polylactic acid matrix, even if this was achieved in (9) by a process of preparing the microspheres which was different from that used in the contested patent. The definition of the microspheres in claim 1 presently on file was, in the respondents' opinion, still such as to call into question their novelty vis-à-vis the prior art of (9).

The respondents submitted that, in their opinion, the prior art of document (14) was sufficiently relevant to put at risk the maintenance of the contested patent. Admission of (14) into the proceedings was therefore, in accordance with the consistent practice of the boards of appeal in such cases, clearly justified.

The respondents argued further that citation (14) already described a solvent evaporation process for the preparation of homogeneous microspheres involving the same procedural steps as the claimed process in the contested patent. Moreover, (14) suggested as active agents to be incorporated into the polymer matrix, in column 5, especially from line 55 onwards, partially the same classes of water-soluble physiologically active substances as in the patent, and referred also in column 3, lines 29 to 33, to polylactide, polyglycolide and copolymers thereof as the preferred matrix materials. The citation referred further in column 2, lines 54 to 55 in conjunction with lines 61 to 62, to tetrahydrofuran, alcohols, water and acetone, which were also mentioned in the contested patent, as suitable solvents for the preparation of the solution containing the active agent. Citation (14) suggested in column 3, lines 4 to 5, even mixtures of the above solvents as an appropriate solvent for the active agent and went on to state in line 16 to 17 that both the active agent and the wall material (matrix) should be in the solvent.

It was also of no relevance that the process of (14) disclosed dissolving or dispersing the active agent in the solution of the matrix material as possible alternatives, because both these alternatives were disclosed as being entirely equivalent. The disclosure of (14) was thus held by the respondents as clearly prejudicial to the novelty of all claims presently on file.

Even if the board came, contrary to the respondents' view, to the conclusion that the subject-matter of the contested patent was not fully anticipated by the prior art of (14), such subject-matter would not involve an inventive step. In this respect, the appellants referred to the Examples (1) and (2) of (14) where a

process for the incorporation of certain active substances into the polylactide type matrix in a molecularly dispersed state was already disclosed. Although in the said examples both the active substance and the matrix material were admittedly hydrophobic and insoluble in water and the solvent used was accordingly methylene chloride, it was in the respondents' opinion merely a matter of routine for the skilled practitioner to adapt the process described in the examples of (14) to the homogeneous incorporation of a hydrophilic and water soluble substance into the hydrophobic an water insoluble matrix by simply using the kind of mixed solvent proposed in the contested patent.

As far as the technical problem addressed by the appellants during oral proceedings in relation to the prior art of (9) was concerned, the respondents submitted that this problem no longer existed, because citation (1) already disclosed microspheres comprising a water soluble active substance and a polylactide matrix which afforded a stable continuous release of the active substance over an extended period of time.

From the foregoing the respondents concluded that the subject-matter of the contested patent, if considered as novel, would not involve an inventive step.

X. The appellants requested that the decision under appeal be set aside and that the patent be maintained with claims 1 to 5 as submitted during oral proceedings and the description as granted with the amendments filed with letter dated 12 May 1998.

XI. Both, respondents 01 and respondents 02 requested that the appeal be dismissed.

Reasons for the Decision

1. *Admissibility of late-filed evidence*

1.1 Document (14) was filed by the respondents during oral proceedings before the opposition division and thus well outside the nine month opposition period provided in Article 99(1) EPC. The appellants, essentially relying on the decisions G 9/91 (OJ EPO 1993, 408), G 10/91 (OJ EPO 1993, 420), G 4/95 (OJ EPO 1996, 412), T 85/93 (OJ EPO 1998, 183), T 1002/92 (OJ EPO 1995, 605) T 258/84 (OJ EPO, 1987, 119) and T 273/84 (OJ EPO 1986, 346), argued that this document had been submitted late pursuant to Article 114(2) EPC. They requested that the case be remitted to the department of the first instance, if the board considered admitting document (14) into the proceedings in view of its possible relevance to the decision in the present case.

Apart from the fact that the decisions relied on by the appellants relate in the first place to the admissibility of evidence filed for the first time in the opposition appeal proceedings and are thus of limited relevance to the present case, the above submission of the appellants, which would *de facto* leave no discretion to the boards of appeal to admit a late filed document into the proceedings, is contrary to the provisions of Article 114(2) EPC, and the legal principle and consistent practice at the EPO in this respect as established, *inter alia*, in Decision G 4/95 (OJ EPO 1996, 412), see Reasons, especially point 4:

"Appeal proceedings are normally examined and decided on the basis of facts and evidence filed during the proceedings before the opposition division. While the filing of facts and evidence by parties to opposition

and opposition appeal proceedings is not precluded at any stage of such proceedings, the **admissibility** of facts and evidence filed at a late stage in such proceedings is always **a matter of discretion for the EPO** (see Article 114(2) EPC)".

1.2 The question before the board is therefore whether the circumstances of the present case justify admission of (14) into the appeal proceedings in accordance with Article 114(1) EPC.

In the present case, the first point to note is that document (14) was already on file during the first instance opposition proceedings and was also referred to in the decision of the opposition division (see Reasons, point 8) by the inclusion of the following statement in the said decision:

"The present decision was made without taking into account the late filed piece of evidence D14".

From this statement it merely follows that the opposition division was able to come to the decision to revoke the patent on the basis of the evidence filed by the respondents before the time limit set in Article 99(1)EPC had expired, but certainly not that (14) was not admitted into the proceedings or that the opposition division did not examine the content of (14) and its possible relevance to the decision.

Moreover, the appellants themselves presented for the first time during the oral proceedings before the opposition division a substantially amended version of claim 1 (see paragraph III above: auxiliary request), which basically corresponds to claim 1 of their present request, in order to avoid revocation of the patent on the grounds of lack of novelty on the basis of the evidence presented by the respondents within the nine

months period for opposition. In view of the substantial amendments to the claims filed at this late stage in the first instance opposition proceedings, the primary purpose and reason for the respondents to submit the additional evidence of (14) was apparently to challenge the amended version of the claims on its merits. Thus, in the board's view, the late filing of document (14) was not deliberate but rather in response to the amended claims and as such does not represent an abuse of the proceedings (see in this respect T 534/89, OJ EPO 1994, 464).

Further to the admissibility of document (14), it also appears important to note that this document had been available to the parties since December 1994, i.e. more than three years before the oral proceedings before the board were held. During this period of time the appellants have exhaustively taken the opportunity to bring their observations and comments concerning the prior art of (14) and its relevance to the present case to the board's attention, namely in the statement of the grounds of appeal filed on 24 May 1995 and in the letters dated 23 January 1996 and 12 May 1998. From this it is evident that the admission of document (14) would not contravene the appellants' rights laid down in Article 113(1) EPC.

1.3 In view of the above considerations, the board has decided to admit document (14) into the proceedings.

2. *Opposition under Article 100(b) EPC*

In the impugned decision (see Reasons, point 3) the opposition division concluded that the respondents' submissions did not provide a reasonable basis for an

opposition under Article 100(b) EPC. The respondents did not raise insufficiency (Article 83 EPC) again as a ground for opposition under Article 100(b) EPC in the appeal proceedings. No further observations in this respect are therefore necessary.

3. *Amendments*

3.1 Compared with claim 1 as granted, the present claim 1 was amended during the appeal proceedings

(i) by the insertion of the feature "wherein the water-soluble physiologically active substance is uniformly incorporated into the polylactic acid", in order to characterise the physical structure of the polymer/active substance matrix; and

(ii) by the additional definition of the claimed microspheres in terms of the process for their preparation.

Amendment (i) is taken from lines 5 to 7 on page 16 of the application as filed. Amendment (ii) refers to the process features disclosed in the first paragraph on page 6 and in claim 5 of the originally filed application documents.

Claim 2 is based on originally filed claim 5 and has been restricted to a process for preparing microspheres with the technical features of claim 1.

Dependent claims 3 to 5 correspond to claims 4 to 6 as originally filed.

3.2 The amended claims are thus adequately disclosed in the originally filed documents. Compared with the claims as granted, the present claims contain at least two additional technical features and therefore confer less protection. Consequently, all claims comply with the provisions of Article 123(2) and (3) EPC.

3.3 The respondents objected during oral proceedings to the clarity of the term "uniformly incorporated" used in the technical feature referred to as amendment (i) in paragraph 3.1 above. However, the originally filed description as a whole and the examples make it sufficiently clear to the skilled reader that the term "uniformly incorporated" refers in fact to the homogeneous, uniform incorporation of the water soluble physiologically active substance in the polylactic acid matrix in **a molecularly dispersed state,** resulting from the step of uniformly dissolving both these components in the particular mixed solvent or the organic acid during preparation of the claimed microspheres. Thus, the amended claims are, in the board's judgment, sufficiently clear and comply, in this formal respect, too with the requirements of Article 84 EPC.

4. *Novelty*

4.1 Citation (9), which was considered by the respondents prejudicial to the novelty of claim 1, refers to the preparation of biodegradable, injectable microspheres comprising copolymers of D,L-lactic acid and glycolic acid (PLGA) (see page 188, left-hand column, first full paragraph) as the matrix and the polypeptide nafarelin as the water soluble physiologically active substance (see the paragraph bridging pages 187 and 188). The particle size of these microspheres of from 10 to 50μm also falls within the range claimed in the patent in suit, and from Figure 1 in the right-hand column on

page 189 of (9) it is derivable that the maximum eluted amount of nafarelin after 24 hours, when determined in **in vitro** elution test corresponding to that used in the present patent, similarly falls within the range specified in claim 1 of the patent in suit.

What is substantially different in the contested patent compared with the prior art of (9) is the method for preparing the microspheres. Thus, the microspheres disclosed in (9) are prepared by a **phase separation process** (see L.M. Sanders et al., J. Pharm. Sci. vol. 73, No. 9, (1984), 1294-1297, especially the paragraph bridging the left-hand and right-hand column on page 1295) comprising the steps of:

(i) co-emulsifying an aqueous solution of nafarelin and a solution of the copolymer in dichloromethane to form a water-in-oil emulsion;

(ii) adding a nonsolvent for the copolymer to precipitate out the copolymer around the aqueous droplets,

(iii) adding the suspension of the semi-formed microspheres to a large volume of non-solvent to cause them to harden and to complete the extraction of dichloromethane; and

(iv) sieving, washing and drying the microspheres.

In contrast to the above method, the claimed microspheres are prepared by a **solvent evaporation process** (see especially page 3, lines 29 to 34, page 5, lines 2 to 49, examples of the patent specification) comprising the steps of:

(i) preparing a solution of the water soluble physiologically active substance and the polylactic acid **uniformly dissolved** in a mixed solvent comprising a hydrophilic organic solvent and water or in an organic acid;

(ii) mixing the solution with a poor solvent which is immiscible with said mixed solvent or organic acid to give an oil-in-oil type or water-in-oil type emulsion; and

(iii) subjecting the mixture to solvent evaporation drying.

4.2 The microspheres claimed in Claim 1 as amended during appeal proceedings are now defined by certain product parameters, such as the composition of the matrix and the nature of the physiologically active substance incorporated therein, the particle size of the microspheres and their physical structure ("uniformly incorporated"), the **in vitro** elution rate of the physiologically active substance in a particular test, and additionally by the method of their preparation (process parameters). In the present case, the process parameters have been included in the independent claim in order to delimit the claimed subject-matter in the patent in suit with respect to novelty from the prior art of (9).

If products cannot adequately be defined or delimited from the state of the art (solely) by their structural characteristics (product parameters) but only by the method of their manufacture (process parameters), novelty can be established only if evidence is provided that the particular method of their preparation results in products which are in fact different from those disclosed in the state of the art. It is sufficient for this purpose if it is shown that distinct differences

exist in the properties of the products. Evidence of novelty, however, cannot involve properties which are not attributable to the product parameters, i.e. which are not inherent in the products themselves (see in this respect Decision T 205/83 (OJ EPO, 1985, 363, Reasons, point 3).

4.3 In the present case, the appellants have presented during oral proceedings elution or release profiles of the microspheres prepared as described in the Examples 1 to 5, 7 and 8 of the patent in suit for comparison with the release profile of nafarelin of document (9) on the basis of the data provided in these documents. From this comparison it is derivable that the claimed microspheres prepared by **the particular solvent evaporation method** specified in present claim (1) altogether show a similar and de facto **continuous release profile** which is distinctly different from the **triphasic release profile** of the microspheres prepared by **the phase separation method** of the prior art of (9). There can also be no doubt that that this substantial difference in drug release in comparison with (9) is due to the particular physical structure of the claimed microspheres in the contested patent resulting from the homogeneous incorporation of the water soluble physiologically active substance in the polylactic acid matrix in a molecularly dispersed state (hereinafter referred to as "homogeneous microspheres"), which in turn results from the step of uniformly dissolving the water soluble physiologically active substance and the polylactic acid matrix in the mixed solvent or in the organic acid in the course of the preparation of the microspheres (see paragraph 4.1 above, step (i)). Taking this into account, the appellants have provided, in the board's judgment, adequate evidence that homogeneous microspheres defined by the technical features of present claim 1 are not anticipated by the prior art of (9).

4.4 The novelty of the claimed microspheres has been disputed by the respondents on the basis of document (14), too. Said document discloses a method of preparing microcapsules laden with an active agent (see claim 1) comprising the steps of:

(i) dissolving or dispersing an active agent in a solvent and dissolving a wall forming material (matrix) in said solvent;

(ii) dispersing said solvent containing said active agent and wall forming material (matrix) in a continuous-phase processing medium;

(iii) evaporating from 10 to 90 weight% of said solvent from said dispersion of step (ii), thereby forming microcapsules containing said active agent in suspension; and

(iv) extracting the remainder of the solvent from said microcapsules.

The board is aware of the fact that (14) refers to "microcapsules" rather than to "microspheres". However, as is clearly stated in document (13) (see especially page 84, line 4 to 5), the terms "microcapsules and "microspheres" have been used interchangeably in the literature. According to (13), when using the solvent evaporation process, homogeneous microspheres will be formed, if the solvent is selected to dissolve both, the active agent and the core material (matrix material). Taking this into account the board considers that document (14), too, is concerned with the preparation of microspheres, which, in cases where the solvent is selected to dissolve both the active agent and the matrix material, are homogeneous microspheres in the sense outlined above but have a different, heterogeneous physical structure in cases where the

solvent is selected to disperse the active agent in the solution of the matrix material (hereinafter referred to as "heterogeneous microspheres" having the active agent dispersed in the matrix in the form of discrete particles rather than in a molecularly dispersed state, see point 4.4 above, step (i)).

4.5 As to the suitable matrix materials, document (14) discloses a non exhaustive list of some twenty different materials which include primarily hydrophilic polymers such as cellulose, acrylic polymers, polysaccharides. etc., in addition to certain hydrophobic polymers, *inter alia*, polylactide, polyglycolide and copolomers thereof (cf. column 3, lines 20 to 33) which fall under the definition of the matrix in the patent in suit.

The physiologically active substance in (14) may be selected from a vast range of primarily water insoluble compounds such as, for example, steroid hormones, lipids, lipoids, prostaglandins, etc. and from certain water soluble substances as well such as, for example, sodium carbonate, salicylates, amino acids, etc. (cf. column 4, line 65 to column 6, line 27).

Apart from the fact that (14) does not necessarily require the step of uniformly dissolving both the active substance and the matrix material in a suitable solvent or solvent system, but discloses dispersing the active substance in the solvent for the matrix material as a suitable alternative, the solvents employed in (14) for the preparation of the solution or dispersion containing the active agent and the matrix are selected from a long list of lipophilic water immiscible solvents such as, for example, halogenated aliphatic and aromatic hydrcarbons but also include alcohols, water and acetone (cf. column 2, lines 54 to 62). In

column 3, lines 4 to 5, it is briefly mentioned that "mixtures of the above solvents can also be used as an appropriate solvent for the active agent", without stating any further details in this respect.

4.6 However, from this broad disclosure of (14) it cannot reasonably be deduced that the microspheres clearly defined in claim 1 of the patent in suit by

- the content of the particular water insoluble, biodegradable polylactic acid type matrix material,
- the content of a water soluble physiologically active substance,
- the particle size of the microspheres,
- the maximum amount of active substance released after 24 hours,
- the particular physical structure,
- and, moreover, the specific method of their preparation, involving the step of uniformly dissolving both the hydrophobic matrix and the hydrophilic active substance in a mixed solvent comprising a hydrophilic organic solvent and water or in an organic acid,

are as such disclosed in document (14).

4.7 In these circumstances the board notes that from document (14) certain embodiments have arbitrarily been selected and combined with each other by the respondents with hindsight to attack the novelty of the subject-matter of the contested patent. Apart from the fact that neither the particle size nor the amount of

active substance which is released within a certain period of time is derivable from (14), the citation does not disclose or in any way suggest the **specific combination of the mandatory features** of present claim 1, as far as the particular hydrophobic, water insoluble matrix material, the hydrophilic, water soluble nature of the physiologically active substance, the manufacturing process and the specific solvent or solvent system used in the manufacture of the claimed microspheres are concerned (see also paragraph 4.6 above).

4.8 In view of the foregoing and in the absence of any other citations submitted by the respondents calling into question the novelty the microspheres according to claim 1 and the method of their preparation according to claims 2 to 5, the board acknowledges the novelty of the subject-matter of the contested patent.

5. *Inventive Step*

5.1 In support of their objection that the subject-matter of the patent in suit lacks an inventive step the respondents relied during oral proceedings on document (1), too, in addition to the prior art of documents (9) and (14).

Both the documents (1) and (9) are concerned with the provision of drug delivery systems (DDS's) for the controlled or retarded release of one and the same class of water soluble physiologically active substances, more specifically polypetides, and both suggest for this purpose DDS's falling under the

general terms "microspheres" or "microcapsules" comprising a polylactide or copolymers of lactic acid and glycolic acid as the matrix material and certain polypeptides as the water soluble physiologically active substance.

In contrast to the claimed microspheres in the patent in suit having the physiologically active substance uniformly incorporated in the matrix in a molecularly dispersed state (homogeneous microspheres; see points 3.3, 4.3 above), document (1) discloses a DDS comprising a spray-dried microsuspension of the active agent in the polylactide matrix, more specifically, a dispersion of discrete particles of the polypeptide with diameters of up to 10μ in the polylactide matrix (heterogeneous microspheres).

Taking into account that both (1) and (9) relate in one way or another to

- DDS's for the controlled or retarded release
- of water-soluble physiologically active substances, selected from the group of polypeptides,
- using a biodegradable hydrophobic polymer of the polylactide or mixed polylactide/ polyglycolide type as the matrix material,

(1) and (9) must be considered to be closer to the subject-matter of the invention than (14), which is entirely silent about a controlled or retarded release DDS comprising the specific combination of a water soluble active substance and a polylactide or mixed polylactide/ polyglycolide type matrix material (see in this respect paragraphs 4.4, 4.5 above).

5.2 Hence, the question which has to be decided is which of the two documents (1) and (9) is more closely related to the subject-matter of the disputed patent. Although the opposition division recognised in its decision (see especially Reasons, point 7) that, compared to the microspheres disclosed in document (9), the claimed ones have a "finer or more homogeneous distribution of the drug" (in other words a different physical structure, homogeneous microspheres), it regarded them in the absence of an unexpected technical effect as a mere alternative to the prior art of document (9) and hence the latter as the most closely related citation.

If on the other hand citation (1) is taken as the basis for comparison, the difference between the DDS it describes and that of the disputed patent lies similarly in the fact that in (1) the active substance is incorporated in the matrix in the form of discrete drug particles (heterogeneous microspheres) rather then uniformly in a molecularly dispersed state as in the contested patent (homogeneous microspheres) and, consequently, also lies in the physical structure.

At first glance, therefore, the decision as to whether to take (1) or (9) as the basis of reference in considering the inventive step of the patent's subject-matter would appear arbitrary. Since in the present case a consideration of the composition and structure of the DDS's disclosed in (1) and (9) in conjunction with their general field of application (controlled or retarded release of a water soluble physiologically active substance) does not help in determining the closest art, the particular properties and application of these prior art disclosed DDS's may possibly provide a key.

As indicated in the patent specification (see especially page 3, lines 8 to 12; page 5, lines 56 to 58, examples) the essence of the invention lies in the provision of a release-controlled polylactic acid type preparation (DDS) which affords a stable, gradual release of active water soluble substances for a long period of time. This view is also supported by the examples in the patent specification which show a stable continuous release of the different active substances at a nearly constant rate over an extended period of time (see in this respect also paragraph 4.3 above).

Taking this stable, continuous release achieved in the present invention into account, the microspheres disclosed in (9) must definitely be eliminated as the closest state of the art on the grounds of the **clearly triphasic nature** of their substance release (see Figure 1). There is a first phase involving an initial rapid release of substance over the first few days. A second phase of very low levels of substance release then ensues and continues until the onset of the third, major phase of substance release.

On the other hand, the clear objective of (1) was the provision of DDS's which afford a **more constant rate of continuous polypeptide release** throughout the entire operational life of the device than could be obtained with previously known biogedradable systems (see especially page 3, lines 46 to 49).

This means that in terms of composition, structure **and** application (properties) citation (9) is less closely related to the patent's subject-matter, while (1), if all of the above aspects are considered, is closer. Citation (1) is therefore taken as the starting point for determining the technical problem underlying the contested patent.

5.3 Citation (1), as has already been said, describes a DDS for the controlled administration of a macromolecular polypeptide having discrete particles of the polypeptide with a diameter of 10 μ or less dispersed in the polylactide or mixed polylactide/polyglycolide matrix. However, the physiologically active water soluble substances which may be incorporated in the DDS of (1) to achieve the desired controlled release are **strictly limited to macromolecular polypeptides having molecular weight greater than 1000,** suitably greater than 10 000 and more preferably greater than 15 000 daltons (see the paragraph bridging pages 5 and 6, claims).

In order to ascertain the technical problem addressed by the disputed patent it has to be asked what by comparison with (1) is achieved by the DDS (microshperes) which the patent describes. The patent specification (see especially page 3 line 35 to page 4, line 40; examples) makes it clear that the water soluble physiologically active substances (drugs) suitable to be incorporated in the matrix to afford their continuous controlled release, are in the present invention neither limited to macromolecular polypeptides nor to a certain minimum molecular weight, but include any drug showing a high hydrophilicity and a low partition rate in oil and water, and may be selected, irrespective of their chemical structure and molecular weight, from broad groups of each of hydrophilic anticancer drugs, antibiotics, polypeptides, antipyretics, sedatives, antiinflammatory agents, antitussives, antiepileptics, antihistaminincs, hypotensives, diuretics, antidiabetics, muscle relaxants, antiulcer agents, antidepressants, antiallergic agents, cardiotonics, antiarrhythmic agents, vasodilating agents, anticoagulating agents, narcotic antagonists, hemmostatic agents, antitubercular agents, steroid hormones, etc.

The technical problem by comparison with (1) may therefore be seen as that of providing a polylactic or polylactide or mixed polylactide/polyglycolide type DDS, which affords continuous release of a water soluble physiologically active substance over an extended period of time at a constant rate throughout the entire operational life of the system, irrespective of the chemical nature, structure and molecular weight of said active water soluble substance.

The solution of the problem lies in the provision of microspheres which have the physiologically active substance (drug) incorporated in the polymer biodegradable polylactide matrix in an entirely uniform molecularly dispersed state in spite of the fact that the drug, on the one hand, is hydrophilic and water soluble, whilst the matrix, on the other, is hydrophobic and insoluble in water.

That the problem posed is indeed solved by the provision of the claimed microspheres is plausibly derivable from the release profiles provided for the Examples 1 to 5, 7 and 8 of the patent in suit which include from a structural point of view such different substances as adriamycin, tobramycin, cisplatin, insulin and calcitonin.

5.4 Neither the technical teaching of citation (1), taken individually, nor its combination with the teaching of citation (14), provides any indication that would lead the skilled person to seek the solution in the provision of the particular homogeneous microspheres according to the invention. Nor is there any indication available in the cited prior art suggesting to a person skilled in the art as to how he could prepare a DDS having the specific properties and capabilities of the claimed microspheres in the patent in suit.

In sharp contrast to the invention, the method of preparing the DDS's of citation (1) essentially involves spray-casting of a micro-suspension of the polypeptide in a solution of the polylactide matrix. In this connection (1) provides the skilled reader under the headline "Methods of Preparation" (see page 8, lines 30) with the teaching that for preparing the solution of the polylactide matrix material "solvents other than acetone or methylene chloride may be used, provided the protein is compatible with, **and insoluble** in, the solvent", thereby excluding any possibility of preparing homogeneous microspheres. The result of this process is necessarily microspheres having a **heterogeneous physical structure** of the polymer/polypeptide matrix. Consequently, the teaching of (1) points away from the possibility of homogeneously incorporating a broad spectrum of hydrophilic drugs in polylactide-type microspheres in a molecularly dispersed state in order to solve the problem and to provide a DDS which affords continuous release of a broad range of substantially different water soluble physiologically active substances over an extended period of time at a constant rate.

This is equally true for Example I A on page 12 of (1), which refers, contrary to the respondents' assertion during oral proceedings, *expressis verbis* to a microsuspension of β-Interferon in a solution of polylactic acid/polyglycolic acid in acetone (see especially page 12, lines 55 to 56), rather than to a uniform solution of both these components.

5.5 Even, if the skilled person had taken the teaching of document (14) into consideration, it would not have provided him with the incentive to solve the problem defined above by the provision of homogeneous

microspheres comprising a hydrophilic active agent and a hydrophobic polylactide type matrix. It is true that (14) discloses in Examples 1 and 2 polylactic acid-type homogeneous microspheres containing **hydrophobic drugs**, namely the steroid hormones progesterone and norgestimate, incorporated in the polymer matrix in a molecularly dispersed state. In both examples methylene chloride is used as the solvent to dissolve both the hydrophobic, water insoluble drug and the hydrophobic, water insoluble matrix.

The skilled person faced with the problem of incorporating a hydrophobic, water soluble drug into a polylactide type matrix would have had no reason or incentive to change the solvent, because (14) teaches dispersing the active agent in the solvent for the matrix material as a suitable alternative even if the result arrived at is heterogeneous microspheres. Similarly, the skilled person could in no other way derive or glean from the disclosure of (1) or (14) taken individually or from their combination any clue leading him to seek the solution of the problem defined above in the preparation of homogeneous microspheres by the solvent evaporation method using the specific mixed solvent system comprising a hydrophilic organic solvent and water or an organic solvent to achieve uniform incorporation of the hydrophilic drug into the hydrophobic matrix in a molecularly dispersed state.

Heterogeneous microspheres disclosed in (9) show a triphasic, discontinuous release profile. Therefore, the skilled person faced with the existing problem of providing a DDS for the controlled, continuous release of an active substance would have disregarded the teaching of citation (9) when seeking in the state of the art a solution to this particular problem.

5.6 The result arrived at, if the view of the appellants and of the first instance was followed and citation (9) was taken as the closest state of the art instead of (1), and if the technical problem was taken as that presented by the appellants during oral proceedings, viz. provision of an improved polylactic or polylactide or mixed polylactide/polyglycolide type DDS, which affords, immediately following its application, continuous release of a water soluble physiologically active substance at a constant rate over an extended period of time, would not lead to a more favourable outcome for the respondents.

5.7 Although it appears derivable from the teaching of document (9) that the triphasic release profile may possibly be desirable in the particular case of the application of the active substance used in (9), viz. nafarelin, which is an agonistic analogue of lutenizing hormone releasing hormone, such triphasic, discontinuous release is certainly unsuitable for the application of the vast majority of drugs which require maintenance of a constant serum level of the drug over an extended period of time. However, citation (9) is entirely silent about any changes in the physical structure or composition of the microspheres which could possibly be made in order to achieve a more continuous release of the drug from the polylactide type matrix.

Even if the skilled person had been aware of the continuous release in (1) and on this basis taken the teaching of citation (1) into consideration, it would not have provided him with the incentive to seek the solution of the problem defined above in the provision of the particular homogeneous microspheres of present claim 1, for the reasons already given in paragraph 5.4 above.

5.8 As explained in more detail in paragraph 5.5 above, document (14) does not suggest the preparation of homogeneous microspheres by the solvent evaporation method using the specfic mixed solvent system comprising a hydrophilic organic solvent and water or an organic solvent to enable incorporating the hydrophilic drug in the hydrophobic matrix in a molecularly dispersed state, and therefore provides no suggestion of solving the technical problem defined above in relation to the prior art of (9) in the manner proposed by the disputed patent.

5.9 In conclusion, none of the documents (1), (9) and (14), taken individually, nor any combination thereof renders, in the board's judgment, the claimed microspheres in the contested patent obvious to a person skilled in the art. The non-obviousness of the microspheres also imparts an inventive step to the method for their preparation according to claims 2 to 5.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent as amended in the following version:

Claims: 1 to 5 as submitted during the oral proceedings

Description: as granted with the amendments as filed with letter dated 12 May 1998.

The Registrar:

P. Martorana

The Chairman:

U. Oswald

GR
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